DNA Analysis of Stool for Colon Cancer Screening (Cologuard®)

Policy MP-006

Origination Date: 06/10/18
Reviewed/Revised Date: 10/22/19
Next Review Date: 10/22/20
Current Effective Date: 10/22/19

Disclaimer:
1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the “Policy” section for more information.

Description:
Colorectal cancer is one of the most preventable cancers, yet cancer is the second leading cause of deaths in the United States. In 2019, there will be an estimated 101,420 new cases of colon cancer and 44,180 of rectal cancer, approximately 51,020 men and women will die from the disease. Without preventive measures, approximately 4-5% of Americans will develop colorectal cancer at some point in their lives. On August 11, 2014, Cologuard® was approved by the FDA. This is the first stool-based colorectal screening test that detects the presence of red blood cells and DNA mutations. Cologuard utilizes a multi-target approach to detect DNA and hemoglobin biomarkers associated with colorectal cancer and pre-cancer.

Eleven biomarkers are targeted and provide a stronger connection between colorectal cancer and pre-cancer. Methylation, mutation, and hemoglobin results are combined in the laboratory analysis to provide a single positive or negative reportable result.

Policy Statement and Criteria

1. Commercial Plans

   U of U Health Plans does NOT cover any other method of DNA analysis of stool testing for colon cancer screening. Use of this testing is considered investigational/experimental.

   U of U Health Plans does NOT cover Cologuard® for stool colon cancer screening as it is considered not medically necessary.
2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at:
http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Clinical Rationale

As with any diagnostic test, the key outcomes are the diagnostic performance (i.e., sensitivity, specificity, positive and negative predictive value) compared to a gold standard, and consideration of how the results of the test will be used to benefit patient management. Of the various screening options (fecal occult blood testing, flexible sigmoidoscopy, double contrast barium enema, colonoscopy), colonoscopy is considered the gold standard. For example, in patients considered at high risk for colorectal cancer, due either to a family history or HNPCC mutation, colonoscopy at varying intervals is recommended by the American Society of Colorectal Surgeons, the American Gastroenterological Society, and the American Cancer Society. Therefore, patients at high risk of colorectal cancer with suspected or known mutations of the HNPCC gene, should have a colonoscopy.

For patients at average risk to moderate risk for colorectal cancer, the above organizations also recommend colonoscopy starting at age 50, with an interval of 10 years, as one screening option. In addition, other screening techniques are also considered options, and the choice of screening option may be dictated in part by patient preference. Many authors have noted the low patient acceptance of current colorectal cancer screening options, particularly flexible sigmoidoscopy and colonoscopy; at the present time only about 40% of eligible patients undergo screening for colon cancer. Advocates of genetic testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations. Therefore, for patients at average to moderate risk of colon cancer, genetic testing of stool samples will be compared to colonoscopy and also to fecal occult blood testing, the other entirely noninvasive technique. Patient acceptance of the different options is also a relevant outcome as a technique to increase screening compliance.

The available published, peer-reviewed data focus on the technical feasibility of genetic testing of stool samples. For example, Ahlquist and colleagues published a study focusing on the use of a multi-target assay panel for colorectal cancer screening. This retrospective study included 22 patients with known colorectal cancer, 11 with adenomas, and 28 patients with normal colonoscopy examinations. It was not reported whether or not these patients were considered at average, moderate, or high risk for cancer. The panel included 15 sites on the KRAS gene, p53 and adenomatous polyposis genes, analysis of BAT-26, and highly amplifiable DNA. The panel detected 20 of the 22 cancers (91%) and 9 of the 11 adenomas (82%). The same panel assay was performed on tissue samples from 19 of the 21 cancers. The presence of point mutations was concordant in tissue and stool analysis in 12 of the 19 paired specimens. The authors attributed the high neoplasm detection rate of the stool analysis to the efficient isolation of human DNA from the stool, but also commented that cancers represented in this study were large (median 4 cm in diameter) and symptomatic, and thus may shed more aberrant DNA than smaller cancers. For the 11 patients with adenomas, the results of the stool DNA testing were compared to fecal occult blood testing. While the fecal occult blood testing was negative in all these patients, genetic mutations were detected in the stool sample of all patients with adenomas.
Dong and colleagues performed a study of stool DNA isolated from 51 colorectal cancer patients. The stool DNA and tumor tissue were evaluated for the presence of mutations in the genes p53, BAT-26, and KRAS. The 3 genetic markers together detected 71% of the 51 patients. Of interest, no genetic mutations were identified in the tumor tissue of 15 patients. Other feasibility studies using a variety of markers have also focused on patients with known cancers, and thus these studies do not duplicate the targeted populations for screening. No prospective studies were found in the published literature comparing the diagnostic performance of analysis of DNA from stool samples to either colonoscopy or fecal occult blood testing among either average to moderate risk to high risk patients. For average risk patients, the published feasibility studies focused on the use of different panels of DNA markers. No study identified focused on the use of the single marker, BAT-26, in patients with known or suspected mutations of the HNPCC gene. No studies discussed how the use of DNA analysis in stool samples might supplant or enhance current screening options.

An UpToDate review of the published literature completed in May 2016, identified one systematic review and 5 primary studies which met inclusion criteria for review. Most prominent of the articles were those by Imperiale et al. and Redwood et al. both related to Cologuard. The systematic review was based primarily on the Imperiale et al. article and concluded that the test is most likely to reduce CRC-related death than FIT but with higher resource utilization. However, this assumption is based on annual, not triennial, administration of the test.

Notably, the study by Imperiale et al., was a non-randomized, cross-sectional, multicenter trial of 9,989 patients who were included in the primary analysis. Results from a single, albeit large, study show that Cologuard has better sensitivity and worse specificity than FIT across various clinical manifestations. The other 2 included studies are 1) a model that is based on incorrect pricing information and 2) a study unique to a specific population no relevant in a broad sense. Though the test has a recommended use of once every 3 years, 1 systematic review illustrated its benefit is best if used annually. This may impact its cost effectiveness in real world settings.

Hayes evaluated blood-based genetic testing for colorectal cancer screening in a Genetic Test Evaluation (GTE) Report (2016). They found one study that examined patients who declined colonoscopy (n=109) and were offered a stool-based test or a blood-based genetic test for CRC screening. Of the 90 patients that elected to undergo blood-based testing, 2 patients had a positive result and proceeded with a colonoscopy, demonstrating a change in patient management. Two additional studies provided information regarding test preference. In the first study, a combined blood-based and stool-based test was preferred over a blood-based test and a stool-based test; in the second study, a SEPT9 blood test was ranked first by the majority of individuals over colonoscopy, sigmoidoscopy, and a stool-based test.

A single, small study evaluating change in patient management and 2 test preference studies do not provide sufficient evidence of clinical utility. Furthermore, these studies do not demonstrate improved outcomes. In the future, blood-based CRC screening may have a role in CRC screening, such as for patients who decline the usual recommended testing techniques; however, there is currently not enough evidence demonstrating a positive change in management or an improvement in outcomes to justify its use without additional studies.

Another Hayes GTE Report (2017) looked at Cologuard® for use as a screening test for colorectal cancer (CRC) in average-risk people age 50 years and older. They concluded that even though Cologuard is FDA approved, there is low-quality evidence for clinical validity and very low-quality evidence for clinical utility. Therefore uncertainty remains as to Cologuard’s performance over time, impact on health outcomes, and its effectiveness relative to other CRC screening methods.
UpToDate 2018 summarizes the implications of "false-positives," abnormal DNA testing in patients who are not found to have colonic lesions on colonoscopy, is uncertain. In a study of screening with three modalities (sDNA, colonoscopy, and FIT) in average-risk patients, nearly 10 percent of those with an entirely negative colonoscopy had a positive stool DNA test. It is not known whether these positive tests are clinically important (e.g., representing carcinomas elsewhere in the gastrointestinal tract) or are false positives. There are no data on the appropriate longitudinal follow-up for an abnormal fecal DNA and a normal colonoscopy follow-up study. Positive results that are not explained by colonoscopy findings may generate unnecessary ongoing surveillance or patient anxiety.

Applicable Coding

**CPT Codes**

81528  
Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result (Cologuard®)

**HCPCS Codes**

No applicable codes

References:

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